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Urine concentration and dilution in the rat: Contribution of papillary structures during high rates of urine flow

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Urine concentration and dilution in the rat: Contribution of papillary structures during high rates of urine flow. To examine the contribution of papillary structures to the overall process of urine dilution and concentration at high rates of flow, studies were performed in unilaterally papillectomized kidneys (PX). Comparison of kidney weights in sham-operated and PX rats revealed a significant reduction in total weight of the latter. Papillary length removed was 3045 ± 423 μm. GFR was reduced by 24% and 45% in sham and PX kidneys when compared to their contralateral controls. Under hydropenic conditions, maximal urine concentrating ability (U_{max}) was comparable in control and sham kidneys but was 59% less in PX kidneys. Fractional sodium excretion during hydropenic conditions was comparable in control and PX kidneys. Nonurea solute [(Na + K) × 2] concentration in the medulla of control and papillectomized kidneys was essentially the same. Free water reabsorption ($T^c_{H_2O}$) as a function of osmolar clearance (C_{Osm}) was comparable in control, sham, and PX kidneys. At C_{Osm} greater than 25%, there was a tencency for $T^c_{H_2O}$ to fall in both control and PX kidneys. Free water clearance (C_{H_2O}) during hypotonic saline diuresis rose in almost linear fashion as a function of urine flow (V) without clear-cut differences between control and PX kidneys. There was, however, a tendency for C_{H_2O} to be slightly higher at any level of V in PX than in control kidneys. These experiments suggest that nephrons with long loops reaching into the papilla and the terminal collecting ducts are not essential for the maximal generation and reabsorption of free water.

Concentration et dilution de l'urine chez le rat: Contribution des structures papillaires au cours des débits uriniares élevés. Afin d'évaluer la contribution des structures papillaires au processus global de dilution et de concentration de l'urine au cours des débits urinaires élevés, les effets de la papillectomie (PX) unilatérale ont été étudiés. La comparaison des poids des reins des rats PX avec ceux ayant subi un simulacre d'intervention (sham) a montré une réduction significative du poids total des premiers. La longueur de papille enlevée était de 3045 ± 423 μm. La filtration glomérulaire était réduite de 24% chez les sham et 45% chez les PX par comparaison avec le rein controlatéral. Dans des conditions d'hydropénie U_{max} est comparable chez les Sham et les contrôles mais diminué de 59% pour les reins PX. L'excrétion fractionnelle de sodium dans les conditions d'hydropénie est comparable pour les reins contrôles et PX. La concentration des solutés non uréiques [(Na + K) × 2] dans la médullaire des contrôles et des PX est semblable. La réabsorption d'eau libre ($T^c_{H_2O}$), au cours de la diurèse hypertonique au sel, exprimée en fonction de la clearance osmolaire (C_{Osm}), est comparable chez les contrôles, les sham et les PX. A C_{Osm} supérieure à 25% il y a une tendance de $T^c_{H_2O}$ à diminuer à la fois chez les contrôles et les PX. La clearance de l'eau libre (C_{H_2O}) au cours de la diurèse hypotonique au sel augmente d'une façon presque linéaire en fonction du débit urinaire (V) sans qu'apparaisse de différence nette entre les reins PX et les contrôles. Il y a, cependant, une tendance de C_{H_2O} à être légèrement supérieure, pour toutes les valeurs de V, pour PX que pour les reins contrôles. Ces expériences suggèrent que les néphrons à anses longues atteignant la papille et les canaux collecteurs à anses longues ne sont pas indispensables à l'excrétion et la réabsorption maximales d'eau libre.

The process of urine concentration and dilution is primarily dependent on active sodium chloride reabsorption by the ascending limb of Henle's loop and ADH-regulated water reabsorption from the collecting duct [1]. Although active removal of solute to the exclusion of water in the thick portion of the ascending limb is now well established, evidence for active reabsorption in the thin portion of the ascending limb has remained elusive. In a series of important experiments, Jamison, Bennet, and Berliner [2] and Jamison [3] performed micropuncture of the papillary structures *in vivo* and demonstrated that ascending thin limbs have a significantly lower osmotic pressure than the fluid of adjacent descending limbs of the loop of Henle. This difference was accounted for almost entirely by a lower sodium concentration. Although this finding is in accord with the proposal of active sodium reabsorption in the thin ascending limb, rigorous analysis of this and other data have failed to prove the presence of such a process in this nephronal structure [4]. Studies on isolated ascending thin limb of Henle's loop have also failed to disclose active transport in this structure [5].

From the data obtained in isolated tubule preparations and in micropuncture studies, Kokko and Rector [6] have proposed a hypothetical model of urine concentration in which active sodium chloride transport need only occur in the thick portion of the ascending limb. In this model, the thin limbs contribute exclusively through their permeability characteristics to urea, which permit the generation of a modest luminal to interstitial osmotic gradient. In another

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model, developed by Stephenson [7], the general characteristics are similar to those proposed by Kokko and Rector. These models are particularly pertinent at low rates of urine flow.

Removal of the papilla discards the thin limbs of many (if not most) juxtamedullary nephrons as well as the terminal collecting duct. This procedure eliminates, therefore, the role of urea "trapping" in the countercurrent system, permitting an evaluation of the capacity for free water excretion and reabsorption of more superficial nephrons independent of urea. We have performed studies in rats in which unilateral papillectomy was carried out in an attempt to determine if this procedure alters urine concentrating and diluting capacity when delivery is increased to the distal nephron.

Methods

Female Wistar rats weighing 150 to 200 g which had been drinking a 5% glucose solution for at least 24 hr were submitted to unilateral papillectomy, utilizing a modification of the technique developed by Bing [8]. Ether anesthesia was used while the left kidney was exposed through a flank incision. The renal pedicle was occluded with a rubber-tipped clamp, with particular care of not including the ureter, and a longitudinal incision between 50 to 75 mm was made along the dorsal aspect of the kidney at a distance of approximately 10 mm from the hilum. Slight compression of the two poles exposed the papilla, which was then amputated utilizing fine iris scissors. The papilla was immediately measured with a micrometer and weighed. The two cut cortical surfaces were approximated, and a thin layer of adhesive (Eastman 910) was applied to the incision. These were held together for 5 to 10 sec, after which the kidney was returned to the retroperitoneal space, the clamp was removed, and the skin incision was closed with stainless steel clips. Sham operations included the entire procedure except that the papilla was not removed. The time to perform papillectomies was between 4 to 6 min, and an identical period of time was allowed to elapse during sham operations. At the end of the surgery, each rat received 0.5 g of streptomycin and 100,000 U of penicillin i.m. The animals were returned to individual cages and were allowed to drink 5% glucose solution for 3 to 4 days to insure that the remaining tubules stay patent. At the end of this time, they were placed again on tap water. Studies were performed 2 to 8 weeks after surgery.

Urine samples were cultured for all animals at weekly intervals after surgery and two days prior to the experiment. In general, these cultures were sterile. Rats with positive urine cultures were not used.

All rats received pentobarbital for the performance of physiological studies. Tracheostomy and catheterization of femoral veins for infusion and femoral artery for blood-letting were performed in all. Studies were conducted in three groups of rats.

Group 1 consisted of 7 unilaterally papillectomized and 5 sham-operated rats. All animals were allowed food *ad lib,* but water was withdrawn for 16 hr prior to sudy. Each animal received 0.5 Pitressin® tannate in oil about 30 min prior to anesthesia. Both ureters were exposed through a midline incision, and the pelvis was cathetierized with PE-50 polyethylene tubing. Urine was collected until 0.2 ml had been obtained from each kidney. The osmolality of this sample was taken as the maximum urine concentrating ability (U_{max}). At the end of the U_{max} collection, each animal received 10 μCi of ^{3}H-inulin followed by an isotonic saline infusion calculated to deliver 10 μCi of ^{3}H-inulin per hr at a rate of 0.01 ml/min. After an equilibration period of 30 min, clearance measurements were done from individual kidneys each 15 min for an hour. The mean of all clearances from each kidney was utilized as the GFR for the organ. Fractional and absolute sodium excretion was also measured in these rats. At the end of the experiment, the kidneys of papillectomized rats were removed, dissected free of all fat and connective tissue, blotted on filter paper, and weighed. In four rats the kidneys were separated into cortex, medulla, and papilla (if present), and the tissue was analyzed for sodium and potassium as previously described [9]. Non-urea solute concentration was calculated as (sodium + potassium) $\times$ 2 in tissue water.

Group 2 consisted of 6 unilaterally papillectomized and 3 sham-operated rats in which free water reabsorption titration curves were performed. These were handled in an identical fashion to group 1 except that at the end of the inulin equilibration period, the rats were infused with 2% saline at increasing rates from 0.05 to 0.5 ml/min. At each new rate of infusion, a time period of 30 min was allowed for equilibration before collections were started. Two additional rats, in which at the time of operation part of the outer medulla was purposely removed in addition to the papilla, were also studied under this protocol.

Group 3 consisted of 8 unilaterally papillectomized and 3 sham-operated rats in which free water clearance titration curves were performed. Rats were given 5% glucose solution as their drinking water for 24 hr prior to the experiment. Food was withheld during this period of time. On the morning of the experiment, distilled water equivalent to 3% of their

body weight was administered by orogastric tube in three divided doses 30 min apart. The animals were anesthetized and given inulin, as in groups 1 and 2. At the end of inulin equilibration, infusions of 0.225% sodium chloride were begun at rates varying between 0.05 to 0.5 ml/min. Equilibration at each new rate of infusion was accomplished as in group 2.

Plasma and urine sodium concentrations were measured by flame photometry. Osmolality was determined by freezing-point depression. Inulin radioactivity was determined by scintillation spectrophotometry. Kidney tissue analysis was done as previously described [9]. Standard statistical analyses were performed, utilizing a program developed by Dr. John I. Thornby at the Houston V. A. Hospital.

Results

Maximal urine osmolality and glomerular filtration rate. In general, the size of the papillectomized kidney was similar to that of control kidneys. Histologically, the papillectomized kidney demonstrated absence of the papilla; however, the demarcation between cortex and outer medulla persisted. In the juxtamedullary area, there were areas of tubular dilatation and atrophy. The collecting ducts were shortened but patent. Table 1 summarizes the changes in weight in control, sham, and PX kidneys. There were no significant differences between sham and control kidneys, while papillectomy led to a weight reduction ($P < 0.02$) as compared to control. The weight of the removed papilla averaged 3.83 ± 0.30 mg, while the length was 3,045 ± 423 μm.

As seen in Table 2, U_{max} in the papillectomized kidney averaged 677 mOsm/kg, which was significantly lower than the value of 1,665 mOsm/kg in the control kidney ($P < 0.01$). U_{max} in the sham-operated kidneys was comparable to that in the control kidney. The mean value for GFR, measured by inulin clearance, was 45% lower ($P < 0.001$) in the papillectomized than the control kidney, while in the sham-operated kidney, GFR was 24% lower ($P <$ 0.001) than in the control kidney. No doubt, the reduction in GFR in the sham rats, which was different from PX rats ($P < 0.05$), is the result of damage to cortical nephrons. This, however, would not be expected to alter the results since similar damage would be expected in the papillectomized rats.

Although absolute sodium excretion (not shown) was lower in the papillectomized than in the control kidney (Table 3), fractional sodium excretion (FE_{Na}) was equal or slightly higher in the papillectomized kidney. Analysis of medullary tissue demonstrated no significant differences in non-urea solute concentration in the two kidneys.

Free water reabsorption ($T^c_{H_2O}$). The capacity to reabsorb solute-free water during increasing levels of hypertonic saline diuresis was measured in 6 unilaterally papillectomized and in 3 sham-operated rats. Values for $T^c_{H_2O}$ as a function of osmolar clearance (C_{Osm}) in control, sham, and papillectomized kidneys for all experiments are shown in Figure 1. $T^c_{H_2O}$ rose continuously as the fractional osmolar clearance rose from 1 to 25% without discernible differences among groups. Only at very high osmolar clearances did fractional $T^c_{H_2O}$ tend to fall in some experiments, but this occurred both in control and papillectomized kidneys. Regression line analysis of these data revealed that the slope of the lines for PX ($y = 2.53 + 0.17x$, $r = 0.42$), sham ($y = 3.52 + 0.21x$, $r = 0.55$) and control ($y = 2.73 + 0.19x$, $r = 0.57$) were

Table 1. Renal tissue weight and papillary length

Kidney weight, *g*		
Sham-operated ($N = 5$)		
Control kidney	1.602 ± 0.352	
Sham kidney	1.501 ± 0.374	NS
Papillectomized ($N = 7$)		
Control kidney	1.497 ± 0.266	
Px kidney	1.034 ± 0.261	$P < 0.02$
Papillary weight, *mg*	3.8312 ± 0.2971	
Papillary length, μ	3045 ± 423	

Table 2. Maximal urine concentrating ability (U_{max}) and glomerula filtration rate[a]

	Control ($N = 12$)	Sham ($N = 5$)	Δ%	Papillectomized ($N = 7$)	Δ%
U_{max}[b], *mOsm/kg*	1,665 ± 335	1,793 ± 484	—	677 ± 132	59
GFR[c], *ml/min*	1.06 ± 0.22	0.81 ± 0.16	24	0.58 ± 0.18	45

[a] All values represent the mean ± SD.
[b] 24 hr's dehydration + 0.5 U Pitressin in oil s.c.
[c] Determined by clearance of ^{3}H-inulin. The average of four clearance periods for each kidney was utilized to represent that organ's GFR.

Table 3. Fractional sodium excretion and tissue non-urea solute concentration[a]

	Control	Papillectomized
FE_{Na}[b], %	0.65 ± 0.42	0.71 ± 0.40
Non-urea solute[c], *mM/kg H_2O*		
Medulla	608 ± 37	617 ± 29.2
Papilla	674 ± 47	—

[a] All values represent the mean ± SD. Non-urea solute was calculated as the sum of (sodium + potassium) × 2 in tissue water.
[b] $N = 7$.
[c] $N = 4$.

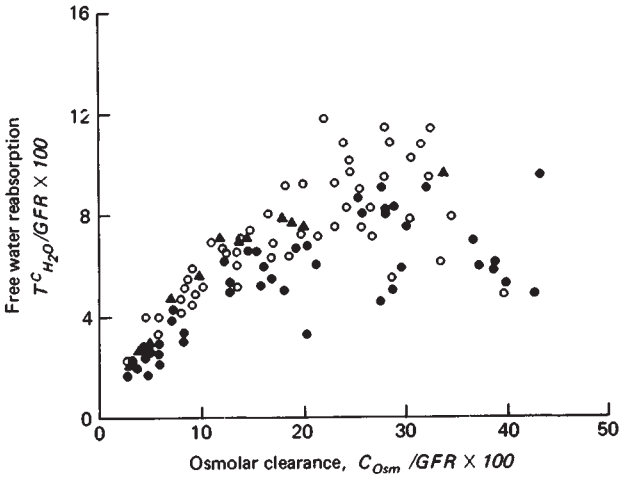

Fig. 1. *Composite plot for all $T^c_{H_2O}$ studies in control (○), sham-operated (▲), and PX kidneys (●).* In the regions demarcated by a C_{Osm} below 10%, many overlapping points have been omitted for clarity of the plot.

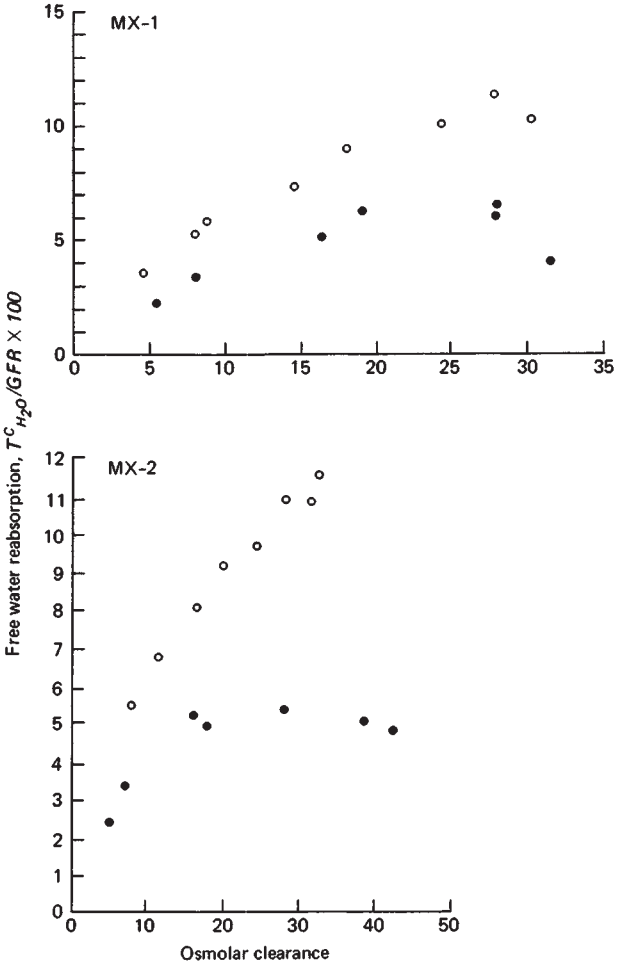

Fig. 2. *T^cH_2O studies in two rats in which medullectomy was performed, demonstrating abnormal $T^c_{H_2O}$ at any level of C_{Osm} when control and PX kidney are compared.*

not significantly different from each other. Sham and PX intercepts were different from each other.

In contrast, as shown in Figure 2, two rats in which the outer medulla had been partially removed demonstrated marked impairment of the $T^c_{H_2O}$ to C_{Osm} relationship.

Free water clearance (C_{H_2O}). A composite plot of all experiments is shown in Figure 3. Fractional free water clearance is plotted on the ordinate; fractional urine flow, an index of distal delivery, is plotted on the abcissa. In control kidneys, fractional free water clearance rose linearly through a range of delivery from 1 to 25% of the filtered load. It appears from this plot that fractional C_{H_2O} at any level of delivery is higher in the papillectomized than in the control kidney. It is clear that the ability of the papillectomized kidney to excrete a maximally diluted urine is at least equal to and may actually exceed that of control or sham-operated kidney.

Discussion

The presence of long nephrons with thin limbs is associated in a number of species with the excretion of urine of maximal concentration [10]. This may be a consequence of *1)* active sodium reabsorption in the thin ascending limb or *2)* passive sodium reabsorption secondary to urea "trapping" in the inner medulla.

Papillectomy, as performed in the present studies, results principally in loss of the terminal portion of the collecting duct and severance of long thin loops of Henle of some juxtamedullary nephrons. Presumably, these nephrons atrophy, reducing the total number of juxtamedullary nephrons. Loss of the terminal collecting duct alone, can explain the low U_{max} found in the papillectomized kidneys. A similar association between removal of the inner medulla and markedly reduced U_{max} has been found in the hamster [11], in the rat [12, 13], and in the dog [14]. A reduction in GFR lowers the concentration of solutes reaching the distal nephron, thereby impairing concentrating ability [15], but this appears to be an unlikely explanation for the low U_{max} in PX. Reduced GFR is usually associated with diminished fractional sodium excretion, yet in PX kidneys FE_{Na} was comparable to that in control kidneys. This implies that distal solute load per nephron is comparable in control and PX kidneys. Wilson [13], using a model similar to the present one, has observed that cortical nephron ablation, which is accompanied by a similar fall in GFR to that of PX, does not result in a fall in U_{max} as great as in PX.

Papillectomy may have influenced U_{max} in three

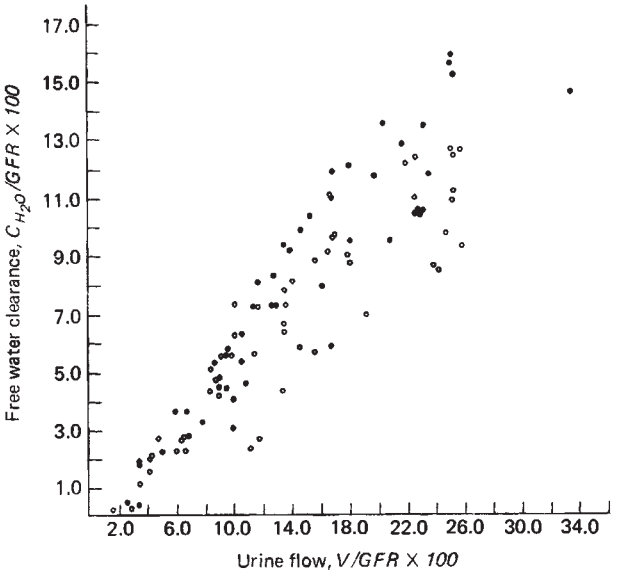

Fig. 3. *Composite plot for all C_{H_2O} studies in control (○) and PX (●) kidneys.* A tendency for C_{H_2O} values in PX kidneys to be higher than in control at any level of V can be noticed.

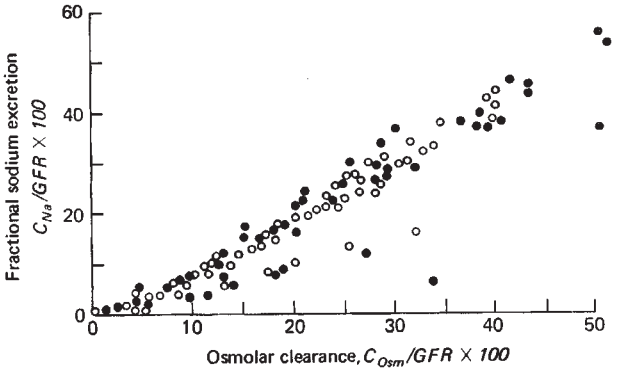

Fig. 4. *Fractional sodium excretion as a function of fractional osmolar clearance in control (○) and PX (●) kidneys.* The magnitude of sodium excretion as osmolar clearance rises is essentially equal in both kidneys.

other ways. First, loss of the distal 10–30% must have reduced the length of reabsorptive epithelium with which the collecting duct fluid comes in contact, thus reducing the reabsorption of both water and urea into the medullary interstitium. Second, ablation of thin limbs may have reduced interstitial osmolality (see above). Finally, loss of the thick ascending limbs of the severed nephrons may have reduced sodium chloride deposition into the outer medulla. Inner medullary urea concentration measured in papillectomized dogs has been shown to be reduced [14]. In the present studies, little urea, if any, remained in outer medullary tissue. Medullary non-urea solute concentration in four rats in which it was measured contributed an average of 617 mOsm/kg H_2O at a time when U_{max} was around 650 mOsm/kg H_2O. Since reduced medullary urea concentration has shown to be associated with a decreased U_{max} [16], this could clearly explain the defect in concentrating ability in PX rats. Diminished non-urea solute concentration in the outer medulla, on the other hand, cannot explain the reduction in U_{max} since this value was not different in control and papillectomized kidneys (Table 3).

The results of the $T^c_{H_2O}$ studies lend support to the critical role of urea in the absence of solute-loading [17, 18] and in the U_{max} defect of PX rats. Under conditions of hypertonic saline diuresis, renal urea concentration is so low that it contributes very little if at all to $T^c_{H_2O}$. Since medullary blood flow is probably maximal under these conditions [19], the main determinants of $T^c_{H_2O}$ are distal sodium chloride reabsorption and collecting duct water permeability. All animals received identical amounts of vasopressin, and solute-loading was comparable; thus, both kidneys should have had identical forces for collecting duct water reabsorption. The similarity of distal solute-loading can be readily appreciated from Figure 4. In both papillectomized and control kidneys, solute delivery was essentially equal without significant differences in the fractional excretion of sodium. This indicates that the major determinant of $T^c_{H_2O}$ was sodium chloride reabsorption in the thick ascending limb. The finding of an essentially normal $T^c_{H_2O}$ to C_{Osm} curve strongly suggest that nephrons with thin loops reaching into the inner medulla are not critical for free water reabsorption with increasing solute load. Since the terminal portions of the collecting ducts were also absent, these do not appear to be essential either. Results similar to those observed in the present studies (low U_{max}, normal $T^c_{H_2O}$) have been obtained by Lief, Sullivan, and Goldberg [20] in a comparable experiment model. In addition, the studies by Tisher [21] in Rhesus monkeys, which lack long thin loops of Henle, also suggest that in this species, these segments are unnecessary for normal urine concentration and $T^c_{H_2O}$ formation.

Wilson [13] has examined the effect on $T^c_{H_2O}$ and C_{Osm} of *isotonic saline* infusion rats. He found that absolute values for $T^c_{H_2O}$ were significantly lower in PX than in control kidneys. This procedure (isotonic volume expansion) in and by itself alters the $T^c_{H_2O}$ to C_{Osm} relationship [22]. Furthermore, if the values obtained by Wilson, corrected for GFR, are plotted along with our data in Figure 1, both control and PX kidneys are indistinguishable from the values obtained in the present study in control, sham, and PX kidneys. Considerable abnormalities in $T^c_{H_2O}$ can

be seen, however, if outer medullary tissue is damaged. When deliberate partial medullectomy was performed in addition to PX (Fig. 2), marked reduction in $T^c_{H_2O}$ at any level of C_{Osm} was observed in experimental kidneys. Under these circumstances, thick ascending limbs and medullary collecting ducts of additional nephrons, including cortical nephrons, were also surely damaged. This may be the explanation for Wilson's findings.

The findings shown in Figures 1 and 2 require further analysis. There was a tendency for $T^c_{H_2O}$ to fall at very high rates of C_{Osm} in all kidneys but particularly in PX and MX. This indicated that "distal disequilibrium" of fluid entering the collecting duct, as has been pointed out by Wallin et al [23], can occur in the rat. Moreover, removal of the distal collecting duct tends to accentuate this problem.

The results of the free water studies emphasize the relatively unimportant role of thin loops of Henle and the terminal collecting duct in the excretion or reabsorption of water at high rates of flow. Throughout a wide range of urine flow rate, urine diluting capacity was similar in control, sham, and PX kidneys. In fact, it appears from Figure 3 that, if anything, C_{H_2O} may have been higher in PX than in control or sham kidneys. This observation appears consonant with the observation of Schnermann et al [24] and Jamison, Buerkert, and Lacy [25] that, despite the absence of ADH, considerable water reabsorption may take place across the distal collecting duct, but this water reabsorption is proportionally greater than sodium reabsorption [24, 25]. Removal of the papilla may have contributed, by ablation of this water reabsorption segment, to the apparent enhancement of C_{H_2O}.

The data from these studies suggest equal concentrating and diluting ability of the two nephron populations. If concentrating ability of juxtamedullary nephrons had been greater than that of superficial nephrons, one would have expected a decrease in the ratio of $T^c_{H_2O}$ to C_{Osm} following removal of papillary structures. The fact that the ratio was unchanged following papillectomy suggests an equal ability of both nephron types to generate $T^c_{H_2O}$ when presented with the same solute load. Thus, the conclusion can not be reached that long-looped nephrons are better concentrators because of an extended eipithelium capable of active sodium chloride reabsorption (the long ascending limb).

Summary. The functional contribution of papillary structures, juxtamedullary nephrons, and terminal collecting ducts to the excretion and reabsorption of free water has been studied. Papillectomy prevents urea-trapping and reduces the length of epithelium available for reabsorption of water across the collecting duct, leading to a reduction in U_{max}. Since fractional free water clearance and fractional free water reabsorption are essentially the same in normal, sham, and papillectomized states, it is suggested that at high rates of urine flow the papillary structures do not contribute significantly to the generation and reabsorption of solute-free water.

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